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Relationship Between Sleep-Disordered Breathing and Neurogenic Obesity in Adults With Spinal Cord Injury

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Spinal cord injury (SCI) substantially increases the risk of neurogenic obesity, diabetes, and metabolic syndrome. Much like in the general population, a discussion of these syndromes in SCI would be incomplete without acknowledging the association of SCI with sleep-disordered breathing (SDB). This article will outline the interplay between obesity and obstructive sleep apnea (OSA), discussing the pathophysiology of obesity in OSA both for the general population and SCI population. The role of insulin resistance in SDB and SCI will also be examined. The epidemiology and pathophysiology of OSA and central sleep apnea in SCI are discussed through an examination of current evidence, followed by a review of central sleep apnea in SCI. Principles of diagnosis and management of SDB will also be discussed. Because sleep deprivation in itself can be a risk factor for developing obesity, the significance of comorbid insomnia in SCI is explored. Ultimately, a thorough sleep history, testing, and treatment are key to improving the sleep of individuals with SCI and to potentially reducing the impact of neurogenic obesity and metabolic syndrome. **Key words:** *central sleep apnea, insulin resistance, metabolic syndrome, obesity, obstructive sleep apnea, sleep apnea syndromes, spinal cord injuries*

Evidence increasingly shows that adults with spinal cord injury (SCI) are at a higher risk of disorders related to metabolic syndrome. The physiologic changes that often occur after SCI, including insulin resistance, obesity, and reduced activity, have been described in detail, including in this issue of *Topics in Spinal Cord Injury Rehabilitation*. One important disease that is increasingly recognized as a comorbidity of metabolic syndrome and obesity is sleep-disordered breathing (SDB).

Overview of Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is the most common type of SDB. It occurs as a result of a repetitive partial or complete obstruction of the upper airway, resulting in reduced airflow that leads to oxygen desaturations and, in the most severe cases, hypercapnia.[1] Apnea is defined as a complete airway collapse for more than 10 seconds. Hypopnea is an airflow reduction of 30% or more with accompanying oxygen desaturation. SDB is confirmed when five or more abnormal breathing events occur per hour of sleep.[2] These events cause multiple microarousals overnight, oftentimes resulting in excessive daytime sleepiness. Moreover, OSA is associated with many serious long-term complications, including increased risk of hypertension, cardiovascular disease, congestive heart failure, stroke, and increased mortality.[1]

The prevalence of obesity in the general adult population is currently approximately 40% but varies by age group.[3] It is estimated that about 3% to 7% of adult men and 2% to 5% of adult women have OSA, though there is concern that this is significantly underreported by as much as 80% in moderate and severe cases of SDB, which would be defined as an apnea-hypopnea index (AHI) of more than 16 episodes of apnea or hypopnea per hour of sleep.[1,2,4] In the general population, obesity is defined based on body mass index (BMI), with 30 to 35 being class 1 obesity (mild), 35 to 40 (moderate), and more than 40 (severe).[3] Obesity has been identified as one of the most important risk factors for sleep apnea. Not only has morbid obesity been shown to result in very high OSA prevalence – between 40% and 90% – but even mild

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and moderate obesity have resulted in increases in prevalence.[5,6,7] The pathophysiology is often related to increased central obesity; in particular, adiposity of the neck can increase the risk of upper airway collapse during sleep, leading to OSA.[8] Neurogenic obesity is the accumulation of adipose tissue due to physiologic changes after SCI.[9] Though neurogenic obesity in SCI is not well studied, it is estimated that about two-thirds of individuals with SCI are obese.[10] The use of the traditional BMI calculation to define obesity is discouraged in individuals with SCI due to differences in body composition compared to the general population.[11] With the larger prevalence of obesity in the SCI population, it could be postulated that there also exists a high prevalence of OSA.

Insulin resistance and type 2 diabetes are frequently comorbid with OSA. OSA is believed to worsen insulin resistance.[6] Diabetes is defined by a glycosylated hemoglobin (HbA1c) of greater than 6.5, a measure of glycemic control over the prior 3 months. The overall prevalence of OSA in the diabetic population is approximately 17%, much higher than the 6% in the general population.[12] Even those with obesity and prediabetes (Hgb A1c of >5.7 but <6.5) are twice as likely to have OSA as those with obesity without diabetes.[13] In a meta-analysis examining almost 6000 patients in prospective cohort studies with OSA, 5.5% had diabetes, with higher incidences in those with worsening OSA severity.[14] Some studies that have sought to diagnose OSA have shown that as many as 95% of patients with diabetes had elevated obstructive AHI on polysomnogram.[15] While this correlation has been widely observed, treatment of OSA with continuous positive airway pressure (CPAP) has not been found to reduce HbA1c, suggesting that either the impact is not reversible or that the two are correlated but not necessarily causative.[16] To date, no studies have investigated if such an association between diabetes and sleep apnea exists specifically in individuals with SCIs.

Epidemiology of Obstructive Sleep Apnea in SCI

Even though the literature currently lacks data connecting various aspects of metabolic syndrome to OSA in SCI, given the shared epidemiologic risk factors in OSA and SCI, there is a high prevalence of OSA in individuals with SCI. As early as 1982, researchers sought to determine whether oxygen desaturation during sleep was a significant problem in individuals with SCI. Braun et al. examined 11 hospitalized patients, seven of whom had cervical complete SCIs. Two of 11 patients desaturated below 90% during sleep. One patient with a thoracic SCI desaturated below 80% during sleep. Braun's group found a correlation between age and oxygen desaturation. They did not assess for a correlation between BMI and oxygen desaturation. Ultimately they concluded that desaturation during sleep was not significantly worse than in the able-bodied population. Of note, this study occurred relatively early on in the recognition of the existence of sleep apnea (the term "sleep apnea" was not even used in this study).[17]

A brief case series published in 1990 that described the impaired sleep of four individuals with SCI found that all of them were eventually diagnosed with OSA. Three had tetraplegia, and one had paraplegia.[18] A study examining older individuals with chronic SCI found that 45% of 22 patients studied had sleep apnea.[19] This parallels trends in the general population that show that OSA increases during middle age.[1]

In 1998, Klefback et al. studied 33 subjects with cervical SCI, finding a prevalence rate of OSA of 15%.[20] In 2000, Burns et al. reported that 40% of 20 individuals with chronic SCI had sleep apnea, with a trend toward increased prevalence in those with tetraplegia.[21] This is consistent with Klefback's study that showed that the American Spinal Injury Association (ASIA) motor score was inversely correlated with severity of sleep apnea.[20] Burns later retrospectively analyzed male military veterans with SCIs. Of 584 patients, 9% had previously been diagnosed with sleep apnea: 14.9% of those with tetraplegia, and 3.7% of those with paraplegia. Additionally, obesity and higher cervical injuries were associated with sleep apnea. However, this study concluded that the number of cases was likely underestimated due to its retrospective nature.[22]

A study in 2017 examined 41 patients with cervical SCIs, conducting polysomnography to identify OSA. Of those patients, 53% were diagnosed with OSA. Three metrics were predictive of a positive test for OSA, including excessive daytime sleepiness, more than three awakenings per night,

and a BMI greater than 30 kg/m^2. While excessive daytime sleepiness and multiple awakenings could be considered consequences of OSA, obesity was the only correlate that could be considered a cause of OSA.[23] In another study, Bauman et al. sought to evaluate the value of home-based diagnostic testing for sleep apnea in individuals with SCI from C1 to T6. In that study, 81.3% of patients were diagnosed with OSA.[24]

Pathophysiology of Obstructive Sleep Apnea in SCI

The pathophysiology of OSA in SCI is likely multifactorial. Given the increase in obesity, insulin resistance, and metabolic syndrome after SCI, there is likely an increased risk of developing OSA. With regard to obesity, both waist and neck circumference have been reported to increase after tetraplegia, contributing to the notion of increasing central obesity in individuals with SCI.[25,26] It has also been suggested that there is a relationship between abdominal girth and sleep apnea. Other studies have also confirmed a link between obesity in SCI and OSA.[22,27]

It has been suggested that unopposed parasympathetic stimulation could result in increased mucosal thickening that may play a role in exacerbating sleep apnea.[28] Additionally, parasympathetic predominance can result in increased secretions after SCI, which may also lead to reduced airway patency.[29]

Although many of the metabolic changes are considered longer term physiologic changes, it has been shown that SDB develops in over half of individuals with tetraplegia within 2 weeks after a SCI, increasing from approximately 10% preinjury to 60% within 2 weeks. That number did increase to 83% by 13 weeks, however it returned to 62% by 1-year postinjury.[26] This suggests that several other mechanisms play a role in OSA in individuals with SCI resulting in such a subacute change. Weakened muscles of respiration, lack of rib cage afferent signals, discoordination of the respiratory muscles, and decreased lung volumes all likely play a part.[30] One study compared the airway anatomy between individuals with tetraplegia, able-bodied subjects without OSA, and able-bodied subjects with OSA, using MRI. It found that airway muscle movement was most similar between those with tetraplegia and able-bodied subjects with OSA, further reinforcing the importance of airway dynamics and negative pressure on development of OSA in those with SCI.[31] The use of different neurodepressants such as benzodiazepines has also been implicated, both in early SCI[26] and in the general population.[32] However, one study in SCI showed no association between OSA and use of either benzodiazepines or baclofen.[23] Further research is warranted to study the impact of different medications and SCI comorbidities on obstructive sleep apnea.

It has also been postulated that changes in ventilatory control may contribute to SDB in SCI. Physiologic changes after SCI, such as a reduced genioglossus reflex to protect the airway or hypoventilation resulting in decrease CO_2 reserve, could potentially increase the risk of SDB, however these hypotheses have not been validated in large studies.[33]

Central Sleep Apnea in SCI

Central sleep apnea (CSA) is a prominent area of concern in individuals with SCI. Studies have identified similarities in the pathophysiology of OSA and CSA, and therefore the two may exist simultaneously.[34] CSA originates from several etiologies that result in the disruption of the motor control of ventilation. These include transient hypocapnia and decreased brainstem output.[34] Additionally, supraspinal neural plasticity rostral to cervical spinal injuries can result in impaired respiratory motor control.[35] Pharyngeal narrowing can also occur during CSA, resulting in a concomitant obstructive picture.[36] Although the impact of such changes in the motor control of respiration may be negligible in those who are healthy, those with preexisting impairment in respiratory mechanics due to SCI may be at a higher risk of developing symptoms of CSA.[34] Several factors may lead to an increased risk of CSA, including changes to chest wall mechanics, impaired cough, and other airway disease.[37] Adding to this, several of the medications used to control spasticity and pain in SCI have central nervous system depressant effects and thus may potentiate CSA.[34,38,39]

In a study by Sankari et al., 77% of patients with chronic SCI had AHIs greater than 5, indicating

SDB. The prevalence was higher in individuals with cervical injuries (93%) compared to thoracic injuries (55%), and it was noted that central sleep apnea (defined as both AHI and central apnea index greater than five events per hour of sleep) was twice as common in the cervical injuries compared to the thoracic injuries.[38] On the other hand, in the study by Bauman, 23.8% of patients had CSA, but level of injury was not delineated.[24] Thus, similar to OSA, even though some studies have shown a correlation between level of SCI and risk of CSA, more research is warranted. With respect to medication impacts on CSA, one study did not show evidence that the use of opiates resulted in CSA.[38] Another study suggested that baclofen may increase the risk of CSA.[24]

Diagnosing and Treating SDB in SCI

Polysomnography (PSG) is the primary method for diagnosis of SDB, with a trend toward at-home studies to reduce barriers to initiating treatment.[40-42] Although a traditional lab-based PSG is the gold standard, functional limitations may make it difficult for those with SCI to participate in such a test. Studies have found at-home PSG testing to be a reliable alternative in the diagnosis of sleep apnea in individuals with SCI.[24] It is also helpful to evaluate the impact of the sleep disorder through validated instruments like the Epworth Sleepiness Scale,[43] the STOP-BANG,[44] and the Berlin Questionnaire.[45] Actigraphy has been used to assess nighttime awakenings in able-bodied subjects, however, it has not been adequately studied in those with paralysis.

Much like in the general population, the gold standard treatment for OSA and CSA is noninvasive positive airway pressure with either CPAP or bilevel positive airway pressure (BiPAP).[46] When one small cohort of eight patients with SCI was offered CPAP, only two tolerated it, and its use resulted in improved daytime alertness.[21] In a later study by the same researcher, 80% of individuals with SCI and OSA were offered CPAP; 63% of those offered were compliant with CPAP, resulting in improved symptoms.[47]

There are other potential treatments for sleep apnea, including dental appliances, hypoglossal nerve stimulation, phrenic nerve pacing, and other surgical procedures,[46,48] however, they have not been adequately studied in SCI. Good sleep hygiene[49] and weight loss through healthy eating and exercise is helpful in many disorders related to metabolic syndrome, and OSA is no exception.[50]

Sleep Deprivation and Metabolic Changes in SCI

Not only can metabolic syndrome lead to sleep disorders, but sleep deprivation is known to be a risk factor for obesity and diabetes.[51] Therefore, sleep hygiene should be evaluated when assessing any patient.[52,53] Changes in several hormones have been observed with sleep deprivation, including increased cortisol[51] and increased thyroid hormone.[54] Studies have identified an increase in ghrelin levels and decrease in leptin levels with sleep deprivation. Ghrelin is known to increase hunger and it spikes before a meal, whereas leptin increases with satiety.[55] The increased ghrelin and decreased leptin levels seen in sleep deprivation can therefore result in increased caloric intake, making it an important driver of obesity.[52] Given the already reduced resting metabolic rate of individuals with SCI,[11] it is all the more imperative to acknowledge the presence of other sleep disorders that can cause sleep deprivation and thus play a role in increasing caloric intake and worsening metabolic disease.

Insomnia disorder is defined as a complaint of dissatisfaction with sleep quantity or quality.[56] Comorbid insomnia, which is insomnia related to other conditions such as mood disorders and pain syndromes, has been described in many with SCI.[19-21,29] In one large study, one-third of individuals with SCI reported sleep difficulties.[57] Patients reported both trouble falling asleep as well as poor sleep, despite sleeping for longer periods of time compared to average sleep durations in the general population.[58] Several SCI-related factors can disrupt sleep for these patients. Pain has been found to be a driving factor; one study found that pain intensity was directly correlated to subjectively worsened sleep quality, anxiety, and depression.[59] Another study identified spasticity, neuropathic pain, and nociceptive pain as drivers of poor sleep after SCI.[58]

Additionally, one study also found that after SCI, the amount of time spent in different sleep stages, known as sleep architecture, can change, leading to less restful sleep.[60] Furthermore, opioids, which are

often used in SCI, can alter sleep architecture.[61] In addition to these intrinsic factors, several aspects of SCI care may result in frequent awakenings overnight. For example, patients are counseled to adjust their positions in bed every 2 hours to prevent pressure injuries. Many with neurogenic bladder are advised to catheterize every 4 to 6 hours to avoid urinary retention.

Other sleep disorders have been characterized after SCI, including periodic leg movements and circadian rhythm disorders.[33] Similar to comorbid insomnia, through sleep disruption, they may potentiate the risk of developing metabolic syndrome; however, no studies have examined the relationship in SCI.

Conclusion

Metabolic syndrome, obesity, and insulin resistance are significant problems in persons with SCI. Not only can all of these factors substantially increase the risk for OSA, but an SCI itself can increase the risk of SDB and comorbidities that can lead to insomnia. Consequentially, having such sleep disorders can also exacerbate metabolic syndrome and obesity, leading to a potentially vicious cycle that should be addressed by clinicians caring for individuals with SCI. Although there is a growing body of literature demonstrating the relationship between SDB and SCIs, there are still gaps in the literature, with a reliance on extrapolating studies about metabolism, metabolic syndrome, and sleep from the general population.

When evaluating a patient with SCI and metabolic syndrome, a detailed sleep history should be obtained to assess sleep hygiene and potential sleep disorders, including assessment of premorbid sleep dysfunction. Clinicians should have a higher index of suspicion in older patients and in those who sustain cervical SCIs. Using one of the instruments mentioned previously may be helpful. Consideration for consulting a sleep specialist should be made. To diagnose sleep disorders, diagnostic workup should include PSG, whether it be in a sleep laboratory or at home. If a patient is diagnosed with a sleep disorder, treatment options should be offered to the patient, most importantly, noninvasive positive airway pressure therapies. Special attention should be paid to the medications and routines of the patient with SCI to minimize the potential for SDB, optimize pain relief, and reduce overnight awakenings. A comprehensive focus on sleep can hopefully improve the overall health and quality of life of the individual with SCI and potentially reduce the impact of the vicious cycle of neurogenic obesity and SDB in SCI.

Conflicts of Interest

The authors declare no conflicts of interest.

REFERENCES

1. Lee W, Nagubadi S, Kryger MH, Mokhlesi B. Epidemiology of obstructive sleep apnea: a population-based perspective. *Expert Rev Respir Med*. 2008;2(3):349-364. doi:10.1586/17476348.2.3.349
2. BaHammam AS, Obeidat A, Barataman K, Bahammam SA, Olaish AH, Sharif MM. A comparison between the AASM 2012 and 2007 definitions for detecting hypopnea. *Sleep Breath*. 2014;18(4):767-773. doi:10.1007/s11325-014-0939-3
3. Centers for Disease Control and Prevention. *Adult obesity facts*. June 29, 2020. Accessed September 15, 2020. https://www.cdc.gov/obesity/data/adult.html
4. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc*. 2008;5(2):136-43. doi:10.1513/pats.200709-155MG
5. Schwartz AR, Patil SP, Laffan AM, Polotsky V, Schneider H, Smith PL. Obesity and obstructive sleep apnea: pathogenic mechanisms and therapeutic approaches. *Proc Am Thorac Soc*. 2008;5(2):185-92. doi:10.1513/pats.200708-137MG
6. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med*. 2002;165(5):677-682. doi:10.1164/ajrccm.165.5.2104087
7. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med*. 2002;165(9):1217-1239. doi:10.1164/rccm.2109080
8. Jehan S, Myers AK, Zizi F, Pandi-Perumal SR, Jean-Louis G, McFarlane SI. Obesity, obstructive sleep apnea and type 2 diabetes mellitus: epidemiology and pathophysiologic insights. *Sleep Med Disord*. 2018;2(3):52-58.
9. Farkas GJ, Gater DR. Neurogenic obesity and systemic inflammation following spinal cord injury: a review. *J Spinal Cord Med*. 07 2018;41(4):378-387. doi:10.1080/10790268.2017.1357104
10. Gater DR. Obesity after spinal cord injury. *Phys Med Rehabil Clin N Am*. 2007;18(2):333-351, vii. doi:10.1016/j.pmr.2007.03.004
11. Farkas GJ, Pitot MA, Gater Jr. DR. A systematic review of the accuracy of estimated and measured resting metabolic rate in chronic spinal cord injury. *Int J Sport Nutr Exerc Metab*. 2019;29(5):548-558. doi:10.1123/ijsnem.2018-0242
12. West SD, Nicoll DJ, Stradling JR. Prevalence of obstructive sleep apnoea in men with type 2 diabetes. *Thorax*. 2006;61(11):945-50. doi:10.1136/thx.2005.057745
13. Fredheim JM, Rollheim J, Omland T, et al. Type 2 diabetes and pre-diabetes are associated with obstructive sleep apnea in extremely obese subjects: a cross-sectional study. *Cardiovasc Diabetol*. 2011;10:84. doi:10.1186/1475-2840-10-84
14. Wang X, Bi Y, Zhang Q, Pan F. Obstructive sleep apnoea and the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. *Respirology*. 2013;18(1):140-6. doi:10.1111/j.1440-1843.2012.02267.x
15. Malik JA, Masoodi SR, Shoib S. Obstructive sleep apnea in type 2 diabetes and impact of continuous positive airway pressure therapy on glycemic control. *Indian J Endocrinol Metabol*. 2017;21(1):106-112. doi:10.4103/2230-8210.196005
16. Labarca G, Reyes T, Jorquera J, Dreyse J, Drake L. CPAP in patients with obstructive sleep apnea and type 2 diabetes mellitus: systematic review and meta-analysis. *Clin Respir J*. 2018;12(8):2361-2368. doi:10.1111/crj.12915
17. Braun SR, Giovannoni R, Levin AB, Harvey RF. Oxygen saturation during sleep in patients with spinal cord injury. *Am J Phys Med*. 1982;61(6):302-9.
18. Bonekat HW, Andersen G, Squires J. Obstructive disordered breathing during sleep in patients with spinal cord injury. *Paraplegia*. 1990;28(6):392-8. doi:10.1038/sc.1990.52
19. Short DJ, Stradling JR, Williams SJ. Prevalence of sleep apnoea in patients over 40 years of age with spinal cord lesions. *J Neurol Neurosurg Psychiatry*. 1992;55(11):1032-6. doi:10.1136/jnnp.55.11.1032
20. Klefbeck B, Sternhag M, Weinberg J, Levi R, Hultling C, Borg J. Obstructive sleep apneas in relation to severity of cervical spinal cord injury. *Spinal Cord*. 1998;36(9):621-8. doi:10.1038/sj.sc.3100675
21. Burns SP, Little JW, Hussey JD, Lyman P, Lakshminarayanan S. Sleep apnea syndrome in chronic spinal cord injury: associated factors and treatment. *Arch Phys Med Rehabil*. 2000;81(10):1334-9. doi:10.1053/apmr.2000.9398
22. Burns SP, Kapur V, Yin KS, Buhrer R. Factors associated with sleep apnea in men with spinal cord injury: a population-based case-control study. *Spinal Cord*. 2001;39(1):15-22. doi:10.1038/sj.sc.3101103
23. Leduc BE, Dagher JH, Mayer P, Bellemare F, Lepage Y. Estimated prevalence of obstructive sleep apnea-hypopnea syndrome after cervical cord injury. *Arch Phys Med Rehabil*. 2007;88(3):333-7. doi:10.1016/j.apmr.2006.12.025
24. Bauman KA, Kurili A, Schmidt SL, Rodriguez GM, Chiodo AE, Sitrin RG. Home-based overnight transcutaneous capnography/pulse oximetry for diagnosing nocturnal hypoventilation associated with neuromuscular disorders. *Arch Phys Med Rehabil*. 2013;94(1):46-52. doi:10.1016/j.apmr.2012.08.215
25. Frisbie JH, Brown R. Waist and neck enlargement after quadriplegia. *J Am Paraplegia Soc*. 1994;17(4):177-8. doi:10.1080/01952307.1994.11735933

26. Berlowitz DJ, Brown DJ, Campbell DA, Pierce RJ. A longitudinal evaluation of sleep and breathing in the first year after cervical spinal cord injury. *Arch Phys Med Rehabil*. 2005;86(6):1193-9. doi:10.1016/j.apmr.2004.11.033
27. Flavell H, Marshall R, Thornton AT, Clements PL, Antic R, McEvoy RD. Hypoxia episodes during sleep in high tetraplegia. *Arch Phys Med Rehabil*. J1992;73(7):623-7.
28. Wasicko MJ, Hutt DA, Parisi RA, Neubauer JA, Mezrich R, Edelman NH. The role of vascular tone in the control of upper airway collapsibility. *Am Rev Respir Dis*. 1990;141(6):1569-77. doi:10.1164/ajrccm/141.6.1569
29. DiMarco A. Respiratory and sleep disorders in spinal cord dysfunction. In: Lin V, Kirshblum S, eds. *Spinal Cord Injury Medicine*. 3rd ed. Demos Medical; 2018.
30. Giannoccaro MP, Moghadam KK, Pizza F, et al. Sleep disorders in patients with spinal cord injury. *Sleep Med Rev*. 2013;17(6):399-409. doi:10.1016/j.smrv.2012.12.005
31. Hatt A, Brown E, Berlowitz DJ, et al. Tetraplegic obstructive sleep apnoea patients dilate the airway similarly to able-bodied obstructive sleep apnoea patients. *J Spinal Cord Med*. 2020:1-11. doi:10.1080/10790268.2020.1829418
32. Roux FJ, Kryger MH. Medication effects on sleep. *Clin Chest Med*. 2010;31(2):397-405. doi:10.1016/j.ccm.2010.02.008
33. Sankari A, Badr MS, Martin JL, Ayas NT, Berlowitz DJ. Impact of spinal cord injury on sleep: current perspectives. *Nat Sci Sleep*. 2019;11:219-229. doi:10.2147/NSS.S197375
34. Badr MS, Dingell JD, Javaheri S. Central sleep apnea: a brief review. *Curr Pulmonol Rep*. 2019;8(1):14-21. doi:10.1007/s13665-019-0221-z
35. Golder FJ, Reier PJ, Bolser DC. Altered respiratory motor drive after spinal cord injury: supraspinal and bilateral effects of a unilateral lesion. *J Neurosci*. 2001;21(21):8680-8689.
36. Sankri-Tarbichi AG, Rowley JA, Badr MS. Expiratory pharyngeal narrowing during central hypocapnic hypopnea. *Am J Respir Crit Care Med*. 2009;179(4):313-319. doi:10.1164/rccm.200805-741OC
37. Sankari A, Vaughan S, Bascom A, Martin JL, Badr MS. Sleep-disordered breathing and spinal cord injury: a state-of-the-art review. *Chest*. 2019;155(2):438-445. doi:10.1016/j.chest.2018.10.002
38. Sankari A, Bascom A, Oomman S, Badr MS. Sleep disordered breathing in chronic spinal cord injury. *J Clin Sleep Med*. 2014;10(1):65-72. doi:10.5664/jcsm.3362
39. Adams MM, Hicks AL. Spasticity after spinal cord injury. *Spinal Cord*. 2005;43(10):577-586. doi:10.1038/sj.sc.3101757
40. Ahmadi N, Shapiro GK, Chung SA, Shapiro CM. Clinical diagnosis of sleep apnea based on single night of polysomnography vs. two nights of polysomnography. *Sleep Breath*. 2009;13(3):221-226. doi:10.1007/s11325-008-0234-2
41. Portier F, Portmann A, Czernichow P, et al. Evaluation of home versus laboratory polysomnography in the diagnosis of sleep apnea syndrome. *Am J Respir Crit Care Med*. 2000;162(3 pt 1):814-818. doi:10.1164/ajrccm.162.3.9908002
42. The impact of split-night polysomnography for diagnosis and positive pressure therapy titration on treatment acceptance and adherence in sleep apnea/hypopnea. *Sleep*. 2000;23(1):17-24. doi:10.1093/sleep/23.1.17
43. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540-545. doi:10.1093/sleep/14.6.540
44. Nagappa M, Liao P, Wong J, et al. Validation of the STOP-Bang Questionnaire as a screening tool for obstructive sleep apnea among different populations: a systematic review and meta-analysis. *PLoS One*. 2015;10(12):e0143697. doi:10.1371/journal.pone.0143697
45. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med*. 1999;131(7):485-491. doi:10.7326/0003-4819-131-7-199910050-00002
46. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med*. 2019;15(2):301-334. doi:10.5664/jcsm.7638
47. Burns SP, Rad MY, Bryant S, Kapur V. Long-term treatment of sleep apnea in persons with spinal cord injury. *Am J Phys Med Rehabil*. 2005;84(8):620-6. doi:10.1097/01.phm.0000171008.69453.b9
48. Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnea: a review. *Sleep*. 2006;29(2):244-262. doi:10.1093/sleep/29.2.244
49. Stepanski EJ, Wyatt JK. Use of sleep hygiene in the treatment of insomnia. *Sleep Med Rev*. 2003;7(3):215-225. doi:10.1053/smrv.2001.0246
50. Strobel RJ, Rosen RC. Obesity and weight loss in obstructive sleep apnea: a critical review. *Sleep*. 1996;19(2):104-115. doi:10.1093/sleep/19.2.104
51. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet*. 1999;354(9188):1435-1439. doi:10.1016/S0140-6736(99)01376-8

52. Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. *Sleep Med Rev.* 2007;11(3):163-178. doi:10.1016/j.smrv.2007.01.002
53. Reiter RJ, Tan DX, Korkmaz A, Ma S. Obesity and metabolic syndrome: association with chronodisruption, sleep deprivation, and melatonin suppression. *Ann Med.* 2012;44(6):564-577. doi:10.3109/07853890.2011.586365
54. Pereira JC, Andersen ML. The role of thyroid hormone in sleep deprivation. *Med Hypotheses.* 2014;82(3):350-355. doi:10.1016/j.mehy.2014.01.003
55. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: A review. *Obes Rev.* 2007;8(1):21-34. doi:10.1111/j.1467-789X.2006.00270.x
56. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Author; 2013.
57. Levi R, Hultling C, Nash MS, Seiger A. The Stockholm Spinal Cord Injury Study: 1. Medical problems in a regional SCI population. *Paraplegia*. 1995;33(6):308-315. doi:10.1038/sc.1995.70
58. Biering-Sørensen F, Biering-Sørensen M. Sleep disturbances in the spinal cord injured: an epidemiological questionnaire investigation, including a normal population. *Spinal Cord.* 2001;39(10):505-513. doi:10.1038/sj.sc.3101197
59. Norrbrink Budh C, Hultling C, Lundeberg T. Quality of sleep in individuals with spinal cord injury: a comparison between patients with and without pain. *Spinal Cord*. 2005;43(2):85-95. doi:10.1038/sj.sc.3101680
60. Adey WR, Bors E, Porter RW. EEG sleep patterns after high cervical lesions in man. *Arch Neurol.* 1968;19(4):377-383. doi:10.1001/archneur.1968.00480040043003
61. Dimsdale JE, Norman D, DeJardin D, Wallace MS. The effect of opioids on sleep architecture. *J Clin Sleep Med.* 2007;3(1):33-36.